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Living Alone and Cardiovascular Disease Outcomes

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DISCLOSURES

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

SG reports no relationships to disclose

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STRUCTURED ABSTRACT

Objective: To evaluate cardiovascular (CV) outcomes in outpatients with coronary artery disease (CAD) living alone compared to those living with others.

Methods: The prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) included outpatients with stable CAD. CLARIFY enrolled participants in 45 countries from November 2009 to July 2010, with 5 years of follow-up. Living arrangement was documented at baseline. The primary outcome was a composite of major adverse cardiovascular events (MACE) defined as CV death, myocardial infarction (MI), and stroke.

Results: Among 32,367 patients, 3,648 patients were living alone (11.3%). After multivariate adjustment, there were no residual differences in MACE among patients living alone compared to those living with others (HR 1.04, 95% CI 0.92-1.18, $p=0.52$), however there was significant heterogeneity in the exposure effect by sex ($P_{\text{interaction}} < 0.01$). Specifically, men living alone were at higher risk for MACE (HR 1.17, 95% CI 1.002-1.36, $p=0.047$) as opposed to women living alone (HR 0.82, 95% CI 0.65-1.04, $p=0.1$), predominantly driven by a heterogeneous effect by sex on MI ($P_{\text{interaction}} = 0.006$). There was no effect modification for MACE by age group ($P_{\text{interaction}} = 0.3$) although potential varying effects by age for MI ($P_{\text{interaction}} = 0.046$) and stroke ($P_{\text{interaction}} = 0.05$).

Conclusions: Living alone was not associated with an independent increase in MACE, although significant sex-based differences were apparent. Men living alone may have a worse prognosis from CV disease than women, further analyses are needed to elucidate the mechanisms underlying this difference.

Trial registration: CLARIFY is registered in the ISRCTN registry of clinical trials (ISRCTN43070564).

Keywords: social isolation, living alone, coronary artery disease, cardiovascular disease

Abbreviations list: chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), coronary artery disease (CAD); coronary artery bypass graft (CABG), cardiovascular disease (CVD), electrocardiogram (ECG), major cardiovascular events (MACE), myocardial infarction (MI), percutaneous coronary intervention (PCI)

Key questions:**What is already known about this subject?**

Patients living alone with coronary artery disease (CAD) may be at increased risk for cardiovascular (CV) events. As individuals with stable CAD live longer with advanced comorbidities, there is an important public health implication to determine if living status is independently associated with poor health outcomes.

What does this study add?

The CLARIFY registry included outpatients with CAD with 5 years of follow-up. Our study suggests that living alone in patients with stable CAD was not associated with an independent increase in major adverse cardiovascular events (MACE), although age and sex-based differences were apparent.

How might this impact on clinical practice?

Elderly patients and women living alone may have potentially lower CV risk, which warrants further confirmation.

Key Message:

- The CLARIFY registry included outpatients with CAD with 5 years of follow-up.
- After multivariate adjustment, there were no differences in MACE among patients living alone compared to those living with others, however there was significant heterogeneity in the exposure effect by sex.
- Men living alone were at higher risk for MACE as opposed to women living alone, driven by a heterogeneous effect by sex on MI ($P_{\text{interaction}}=0.006$).
- There was no effect modification for MACE by age group ($P_{\text{interaction}}=0.3$) although potential varying effects by age for MI ($P_{\text{interaction}}=0.046$) and stroke ($P_{\text{interaction}}=0.05$).
- Future large studies in patients with established CAD will evaluate patient social isolation using validated tools/scoring system, which will inform health care practitioners of patients with potential increased long-term CV risk, as well assist in forming beneficial psychosocial interventions.

INTRODUCTION

Social isolation refers to the lack of contact an individual has with society, with living alone frequently used as a surrogate.(1) Living alone may lead to poor outcomes in patients with coronary artery disease (CAD) through a complex interaction between increased neurohormonal stress with accelerated atherosclerosis, less adherence to guideline recommended therapy and secondary prevention targets, increased anxiety and depression leading to more psychological distress, poor coping mechanisms/self-care, and less access to health care services.(2, 3) Previous analyses have sought to gain insight into the risk of living alone in patients with established cardiovascular disease (CVD). The effect of living alone has been variable due to the significant heterogeneity amongst the populations studied, with sub-group analysis showing potential effect modification by age and sex, and potential lower risk among women and elderly patients living alone.(4-7)

Patients with CAD are diverse with differences in ethnicity, socioeconomic status, location, and psychosocial factors which may play a role in the risk of recurrent CV events.(8) The prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) was initiated to improve knowledge about patients with stable CAD from a broad geographic perspective.(9) As individuals with stable CAD live longer with advanced comorbidities, there is an important public health implication to determine if living status is independently associated with poor health outcomes. The objective of this analysis was to determine, in a stable CAD population, if living alone is

associated with increased CV risk. Given previous research, effect modification by sex and age group were further explored in this post-hoc analysis.

METHODS

STUDY DESIGN AND PATIENT SELECTION

The CLARIFY study cohort included outpatients with stable CAD with 5 years of follow-up, the study methods and design were previously published.(9-12)

Patients eligible for enrolment were those with stable CAD diagnosed by at least one of the following: 1) documented myocardial infarction (MI) (>3 months ago); 2) coronary stenosis >50% on coronary angiography; 3) chest pain with myocardial ischemia determined by stress electrocardiogram (ECG), stress echocardiography, or myocardial imaging; or 4) history of revascularization by coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) (performed >3 months ago). Patients hospitalized for CVD within the previous 3 months (including for revascularization), patients for whom revascularization was planned, and patients with conditions expected to hamper participation of 5-year follow-up were excluded from participating in the study. A total of 32,703 subjects were enrolled in 45 countries, from November 2009 to July 2010 (**Table S1**).

DATA COLLECTION

The investigators completed standardised electronic case report forms at baseline and yearly at each visit for up to 5 years. Living arrangement status was

documented as either “living alone” or “not living alone” at baseline. Further information collected at baseline included demographics; prior medical history and cardiovascular risk factors; current symptoms; physical examination; laboratory values (e.g., fasting blood glucose, hemoglobin A1c [HbA1c], cholesterol, triglycerides); and current chronic drugs regimen (i.e., those taken regularly by the patient for ≥ 7 days before entry in the registry). Data was recorded if an ECG was available for whether the patient was in sinus rhythm, atrial fibrillation/atrial flutter, paced rhythm, or left bundle branch block (LBBB). The remaining patients may not have had ECG data available or may be in another rhythm than above. Investigators reported number of vessels with disease and number of coronary territories with significant stenosis ($>50\%$) independent of whether the patient had a recent angiogram (within 12 months). This data was investigator reported independent of the most recent available angiogram results and may not be mutually exclusive.

For patients missing the yearly in-person visit, telephone contact with the patient, a designated relative or contact, or their physician was attempted. To ensure data quality, onsite-monitoring visits of 100% of the data in 5% of centres were selected at random, regular telephone contact with investigators to reduce missing data and loss to follow-up, and centralised verification of the electronic case report forms for completeness, consistency, and accuracy were undertaken.

OUTCOMES

At each annual follow-up visit, clinical outcomes occurring during the previous 12

months were recorded. The primary outcome of this analysis was major adverse cardiovascular events (MACE), which included CV death, nonfatal or fatal MI, and nonfatal or fatal stroke. Secondary outcomes were all-cause death, CV death, MI, stroke, unstable angina, and major bleeding (defined as leading to hospitalization or transfusion). CV death was defined as fatal MI or stroke, other CV death or death due to unknown cause; any MI or stroke followed by death in the subsequent 28 days was considered fatal. Events were accepted as reported by patients and physicians, without central adjudication, however all events were source verified during audits.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the National Research Ethics Service, Isle of Wight, Portsmouth and Southeast Hampshire Research Ethics Committee, UK. Approval was also obtained in all participating countries, in accordance with local regulations before recruitment of the first participant. All patients gave written informed consent to participate, in accordance with national and local guidelines. There was no patient/public involvement in this research study. CLARIFY is registered in the ISRCTN registry of clinical trials (ISRCTN43070564).

STATISTICAL ANALYSIS

All CLARIFY data were collected and analyzed at an independent academic statistics center at the Robertson Centre for Biostatistics, University of Glasgow, UK, which was responsible for managing the database, performing all analyses

and data storage. Baseline variables are summarized as means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous data, depending on the distribution of the data; and as counts and percentages for categorical data. In this post-hoc analysis, differences between patients living alone and those living with others were compared using Chi-squared tests or Fisher's exact test for categorical variables as appropriate, and 2 sample t-tests or Wilcoxon Mann-Whitney tests for continuous variables, depending on the distribution of the data. A Cox proportional hazards model was used to assess the risk associated with living alone and time to first cardiovascular outcomes. Crude and multivariable adjusted hazards ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated after adjustment for age, sex, and geographic region; as well as baseline history of smoking, diabetes, peripheral arterial disease, MI, PCI, CABG, asthma/chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF). Additional clinical characteristics were also adjusted for, including baseline systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction, and number of vessels with coronary artery stenoses. Heterogeneity was assessed with interaction testing between living status and sex, age group (<65 years, 65–74 years, ≥75 years), and history of prior MI at baseline for primary and secondary endpoints after multivariable adjustment. All p-values for the Cox proportional hazards models were obtained using the Wald test.

RESULTS

A total of 32,367 patients were eligible for inclusion in the analysis with 3,648 patients documented as living alone (11.3%) and 28,728 (88.8%) patients living with others. **Table 1** and **Table 2** includes baseline characteristics, study inclusion, previous medical history, CV risk factors, and symptom profile. The mean age for patients living alone was 67 (± 10.66) years. Patients living alone were older, more likely to be female, predominantly white, less likely to be employed full time, and more likely to be retired than those living with others. More patients living alone were current smokers, had a history of atrial fibrillation, prior HF hospitalisation, history of peripheral arterial disease, and yet had less diabetes. **Table 3** describes cardiovascular therapies. There was a high use of guideline recommended pharmacologic therapy in both groups, there was a lower number of patients living alone taking thienopyridines, beta-blockers, and statins.

Table 1. Baseline Characteristics by Living Arrangement Status

	Living alone (n=3648)	Not living alone (n=28,728)	p-value
Age (years), mean (SD)	67.2 (10.7)	63.8 (10.4)	<0.001
Males (%)	2254 (61.8)	22857 (79.6)	<0.001
Body Mass Index (kg), median (25 th , 75 th quartiles),	27 [25, 31]	27 [25, 30]	0.032
Waist Circumference (cm), median (25 th , 75 th quartiles)	96 [88, 105]	97 [89, 105]	0.01
Ethnicity (%)			
White	2644 (72.5)	18304 (63.8)	<0.001
South Asian	130 (3.6)	2285 (8.0)	
Chinese	167 (4.6)	2573 (9.0)	

Japanese/Korean	142 (3.9)	893 (3.1)	
Hispanic	110 (3.0)	1458 (5.1)	
Black/African	44 (1.2)	294 (1.0)	
Unknown	411 (11.3)	2921 (10.2)	
Employment status (%)			
Employed full-time	605 (16.6)	7291 (25.4)	<0.001
Employed part-time	227 (6.2)	2022 (7.0)	
Unable to work	146 (4.0)	1119 (3.9)	
Unemployed	143 (3.9)	1689 (5.9)	
Retired	2415 (66.2)	15505 (54.0)	
Other	112 (3.1)	1101 (3.8)	
Education level (%)			
Primary school (or less)	1011 (27.7)	7561 (26.3)	<0.001
Secondary school	1785 (49.0)	13251 (46.1)	
College/University	852 (23.4)	7913 (27.6)	
Medical History (%)			
Myocardial Infarction	2150 (59.0)	17251 (60.0)	0.20
PCI	2051 (56.2)	16906 (58.9)	0.003
CABG	907 (24.9)	6722 (23.4)	0.049
Hospitalization for CHF	218 (6.0)	1294 (4.5)	<0.001
Internal Cardiac Defibrillator	65 (1.8)	342 (1.2)	0.003
Pacemaker	124 (3.4)	653 (2.3)	<0.001
Aortic abdominal aneurysm	70 (1.9)	424 (1.5)	0.040
Carotid Disease	350 (9.6)	2107 (7.3)	<0.001
Peripheral Arterial Disease	425 (11.7)	2777 (9.7)	<0.001
Transient Ischemic Attack	137 (3.8)	856 (3.0)	0.010
Stroke	166 (4.6)	1135 (4.0)	0.082
Atrial Fibrillation/Flutter	324 (8.9)	1960 (6.8)	<0.001
Family History of Premature CAD	1120 (30.7)	8096 (28.2)	0.001
Treated Hypertension	2638 (72.3)	20351 (70.9)	0.066
Diabetes	977 (26.8)	8415 (29.3)	0.002
Dyslipidemia	2773 (76.0)	21485 (74.8)	0.109
Asthma/COPD	363 (10.0)	2031 (7.1)	<0.001
Smoking status (%)			

Current	536 (14.7)	3501 (12.2)	<0.001
Former	1505 (41.3)	13468 (46.9)	
Never	1607 (44.0)	11759 (40.9)	
Alcohol intake (number of drinks per week) (%)			
0	1741 (47.7)	13684 (47.6)	0.032
>0 and <20	1745 (47.8)	14025 (48.8)	
20-40	144 (4.0)	921 (3.2)	
>40	18 (0.5)	93 (0.3)	
Stimulant drinks consumed (%)			
Coffee	1789 (49.1)	13551 (47.2)	<0.001
Tea	1200 (32.9)	8781 (30.6)	
Neither	658 (18.0)	6380 (22.2)	
Daily intake of stimulant drinks (cups/day), median (25 th , 75 th quartiles)	2 [2, 4]	2 [2, 4]	0.011
Physical Activity (%)			
No physical activity weekly	639 (17.5)	4584 (16.0)	0.023
Light physical activity most weeks	1850 (50.7)	14782 (51.5)	
At least 20 minutes vigorous physical activity once or twice a week	567 (15.6)	4860 (16.9)	
At least 20 minutes vigorous physical activity at least three times a week	591 (16.2)	4495 (15.7)	
CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CCS, Canadian Cardiovascular society; DBP, diastolic blood pressure; ECG, electrocardiogram; HBA1C, hemoglobin A1C, LBBB, left bundle branch block; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure			

Table 2. Baseline Cardiovascular Characteristics by Living Arrangement**Status**

	Living alone (n=3648)	Not living alone (n=28,728)	p-value
Any angina (%)	840 (23.0)	6328 (22.0)	0.17
Angina and CCS Class			0.13
No Angina	2807 (77.0)	22399 (78.0)	
Angina CCS Class I	263 (7.2)	1788 (6.2)	
Angina CCS Class II	417 (11.4)	3396 (11.8)	
Angina CCS Class III	150 (4.1)	1075 (3.7)	
Angina CCS Class IV	10 (0.3)	68 (0.2)	
CHF symptoms including NYHA class			0.89
No CHF (%)	3098 (84.9)	24375 (84.9)	
CHF NYHA Class II	456 (12.5)	3642 (12.7)	
CHF NYHA Class III	94 (2.6)	709 (2.5)	
Heart Rate (palpation), mean	68.3 (10.6)	68.2 (10.6)	0.79
SBP (mm Hg), mean	132.2 (17.2)	130.9 (16.6)	<0.001
DBP (mm Hg), mean	76.9 (10.1)	77.3 (10.0)	0.020
Left Ventricular Ejection Fraction (%), mean	56.5 (11.3)	56.0 (11.0)	0.032
Number of vessels with disease (%)*			0.005
0	139 (4.6)	864 (3.5)	
1	1279 (41.9)	10053 (40.9)	
2 or more	1634 (53.5)	13649 (55.6)	
Coronary territories with stenosis >50% (%)*			
Left Main	335 (9.2)	2500 (8.7)	0.33
Left anterior descending	2075 (56.9)	16827 (58.6)	0.051
Circumflex artery	1208 (33.1)	10468 (36.5)	<0.001
Right coronary artery	1520 (41.7)	12590 (43.8)	0.013
Bypass Graft	299 (8.2)	2300 (8.0)	0.69
No significant stenosis	146 (4.0)	906 (3.2)	0.007
Coronary angiography not performed (within 12 months)	586 (16.1)	4138 (14.4)	0.007
**ECG Rhythm (%)			<0.001
Sinus rhythm	2462 (93.1)	20499 (95.2)	

Atrial Fibrillation/Flutter	121 (4.6)	702 (3.3)	
Paced rhythm	62 (2.3)	332 (1.5)	
LBBB	158 (6.0)	1025 (4.8)	0.0063
HbA1C (%), mean (SD)	6.7 (1.2)	6.8 (1.8)	0.018
Creatinine (mmol/L), median (25 th , 75 th quartiles)	87 [74, 100]	88 [76, 102]	<0.001
Hemoglobin (g/dL), median (25 th , 75 th quartiles)	13.9 [12.9, 14.9]	14.1 [13.0, 15.0]	<0.001
Fasting Blood Glucose (mmol/L), median (25 th , 75 th quartiles)	5.6 [5.0, 6.5]	5.7 [5.1, 6.7]	<0.001
Total Cholesterol (mmol/L), median (25 th , 75 th quartiles)	4.4 [3.7, 5.1]	4.3 [3.7, 5.0]	0.002
HDL (mmol/L), median (25 th , 75 th quartiles)	1.2 [1.0, 1.5]	1.1 [1.0, 1.4]	<0.001
LDL (mmol/L), median (25 th , 75 th quartiles)	2.37 [1.89, 2.94]	2.37 [1.90, 2.94]	0.68
Fasting Triglycerides (mmol/L), median (25 th , 75 th quartiles)	1.39 [1.00, 1.88]	1.40 [1.02, 1.93]	0.15
<p>CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CCS, Canadian Cardiovascular society; DBP, diastolic blood pressure; ECG, electrocardiogram; HBA1C, hemoglobin A1C, LBBB, left bundle branch block; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure</p> <p>* Investigators reported number of vessels with disease and number of coronary territories with significant stenosis (>50%) independent of whether the patient had a recent angiogram (within 12 months). This data was investigator reported independent of the most recent available angiogram results and may not be mutually exclusive.</p> <p>** Data was recorded if an ECG was available for whether the patient was in sinus rhythm, atrial fibrillation/atrial flutter, paced rhythm, or left bundle branch block (LBBB). The remaining patients may not have had ECG data available or may be in another rhythm than above.</p>			

Table 3. Medications and Reimbursement Status at Baseline by Living Arrangement Status

	Living alone (N = 3648)	Not living alone (N = 28728)	p-value
Medication (%)			
Aspirin	3154 (86.5)	25257 (87.9)	0.011
Thienopyridine	835 (22.9)	7944 (27.7)	<0.001
Other Antiplatelets	291 (8.0)	2695 (9.4)	0.006
≥2 antiplatelets	3644 (99.9)	28721 (99.9)	<0.001
Oral anticoagulants	299 (8.2)	2331 (8.1)	0.87
Beta-Blockers	2652 (72.7)	21718 (75.6)	<0.001
Symptoms indicative of intolerance or contraindication to Beta-Blockers	516 (14.2)	4167 (14.5)	0.56
Ivabradine	330 (9.1)	2873 (10.0)	0.069
Calcium antagonists	1057 (29.0)	7765 (27.0)	0.012
ACE inhibitor or ARB	2790 (76.5)	21902 (76.2)	0.73
Lipid-lowering drugs	3301 (90.5)	26598 (92.6)	<0.001
Statins	2954 (81.0)	23886 (83.2)	0.001
Long-acting nitrates	764 (21.0)	6313 (22.0)	0.16
Other antianginal agents	491 (13.5)	4030 (14.0)	0.36
Diuretics	3154 (86.5)	25257 (88.0)	0.011
Other antihypertensive agents	283 (7.8)	1946 (6.8)	0.027
Digoxin and derivatives	108 (3.0)	706 (2.5)	0.067
Amiodarone/Dronedarone	111 (3.0)	835 (2.9)	0.64
Other antiarrhythmics	46 (1.3)	260 (0.9)	0.036
NSAIDs	237 (6.5)	1350 (4.7)	<0.001
Antidiabetic agents	802 (23.0)	7126 (24.8)	<0.001
Proton pump inhibitors	987 (27.1)	7029 (24.5)	<0.001
Thyroid HRT	263 (7.2)	1144 (4.0)	<0.001
HRT in post-menopausal women	16 (0.4)	82 (0.3)	0.11
Erectile Dysfunction	60 (2.7)	459 (2.0)	0.04
Reimbursement of cardiovascular agents (%)			<0.001
Fully reimbursed	1612 (44.3)	11044 (38.5)	
Partly reimbursed	1363 (37.5)	10880 (37.9)	
Not reimbursed	665 (18.3)	6786 (23.6)	

In unadjusted models, patients living alone had a higher risk of the primary endpoint of MACE (10.3% vs 8.5%, HR 1.24, 95% CI 1.11-1.38, p<0.001), all-cause death (9.8% vs 7.6%, HR 1.31, 95% CI 1.17–1.47, p<0.001), CV death

(6.5% vs 4.8%, HR 1.37, 95% CI 1.20-1.58, $p<0.001$), and stroke (2.7% vs 2.0%, HR 1.35, 95% CI 1.09-1.67, $p=0.006$). There was no difference in rates of MI, unstable angina, major bleeding or hospitalization for CHF (**Table 4**). After adjustment for age and sex, there remained statistically significant differences in the all-cause and CV death outcomes; following additional multivariate adjustment, there were no residual differences in outcomes in patients living alone compared to those living with others (**Table 4**).

Table 4. Comparison of 5-year Cardiovascular Event Rates by Living Arrangement Status

Outcome	5-year event rate (%)		Time to First Event HR (95% CI)		
	Living Alone (N=3,648)	Not Living Alone (N=28,728)	<i>Unadjusted</i>	<i>Adjusted (age and sex)</i>	<i>Adjusted*</i>
MACE	10.3%	8.5%	1.24 (1.11 - 1.38), $p<0.001$	1.11 (0.99 - 1.24), $p=0.07$	1.04 (0.92 - 1.18), $p=0.52$
All-cause death	9.8%	7.6%	1.31 (1.17 - 1.47), $p<0.001$	1.13 (1.01 - 1.26), $p=0.04$	1.08 (0.95 - 1.23), $p=0.25$
CV death	6.5%	4.8%	1.37 (1.20 - 1.58), $p<0.001$	1.18 (1.02 - 1.35), $p=0.02$	1.12 (0.95 - 1.32), $p=0.17$
MI	3.5%	3.4%	1.04 (0.86 - 1.25), $p=0.70$	1.01 (0.84 - 1.22), $p=0.93$	0.97 (0.78 - 1.19), $p=0.76$
Stroke	2.7%	2.0%	1.35 (1.09 - 1.67), $p=0.006$	1.15 (0.93 - 1.43), $p=0.20$	1.00 (0.77 - 1.30), $p=0.99$
Unstable angina	10.8%	11.0%	0.99 (0.89 - 1.10), $p=0.86$	0.97 (0.87 - 1.08), $p=0.55$	0.99 (0.88 - 1.12), $p=0.91$
Major bleeding	1.4%	1.4%	1.01 (0.75 - 1.35), $p=0.96$	0.90 (0.67 - 1.21), $p=0.48$	0.91 (0.66 - 1.24), $p=0.55$

Hospitalization for CHF	5.6%	5.2%	1.10 (0.95 - 1.28), p=0.20	1.02 (0.87 - 1.18), p=0.83	1.07 (0.89, 1.27), p=0.48
*multivariate analysis adjusted for age, sex, geographical region, smoking status, diabetes, peripheral arterial disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, asthma/chronic obstructive pulmonary disease, congestive heart failure, systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction, number of vessels with coronary artery stenosis. MACE reported as a composite of CV death, MI, or stroke. Abbreviations: CHF, congestive heart failure; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction					

Nevertheless, there was significant heterogeneity identified in the exposure effect by sex ($P_{\text{interaction}} < 0.01$) (**Figure 1**). Specifically, men living alone were at higher risk for MACE (HR 1.17, 95% CI 1.002–1.36, $p=0.047$) as opposed to women living alone (HR 0.82, 95% CI 0.65–1.04, $p=0.099$). This difference was primarily driven by effect modification by sex for MI ($P_{\text{interaction}} = 0.006$) with no difference in CV death ($P_{\text{interaction}} = 0.075$) and stroke ($P_{\text{interaction}} = 0.99$). Women living alone in comparison to women living with others showed a significantly lower adjusted risk of MI (2.2% vs 3.2%, HR 0.54, 95% CI 0.35–0.84, $p=0.007$) that was not apparent in males (4.0% vs 3.2%, HR 1.17, 0.92–1.49, $p=0.19$).

The effect of living alone for MACE was consistent across age groups (<65 years, 65–74 years, ≥ 75 years, $P_{\text{interaction}} = 0.33$). There were potential varying effects of living alone by age group for MI ($P_{\text{interaction}} = 0.046$) and stroke ($P_{\text{interaction}} = 0.05$) (**Figure 2**). Specifically, the risk of MI tended to be lowest among older patients (≥ 75 years) living alone in comparison to older patients living with others (3.3% vs 4.2%, HR 0.67, 95% CI 0.43–1.04, $p=0.077$),

intermediate risk among middle age (65-74 years) patients (2.9% vs 3.4%, HR 0.83, 95% CI 0.57–1.21, $p=0.33$), and highest among younger (<65 years) patients in the cohort (3.9% vs 2.9%, HR 1.31, 95% CI 0.96-1.78, $p=0.088$). Similar findings were observed for stroke (**Figure 2**). The effect of living alone was consistent in patients with and without prior MI ($P_{\text{interaction}}=0.44$).

DISCUSSION

CLARIFY is the largest international registry to describe the association of living alone with CV outcomes in a contemporary population of patients with stable CAD. Despite an indication that people living alone had a higher incidence of several outcomes in unadjusted analyses including the primary endpoint of MACE, the results of the adjusted analysis revealed no independent risk of MACE in patients living alone. A novel aspect to our analysis is that we did observe potential sex-based heterogeneity for the effects of living alone. Specifically, women living alone had a trend towards lower risk of MI compared with women or men living with others. Older patients living alone demonstrated a trend towards a lower risk of MI and stroke, while the trends reversed for younger patients living alone.

Recent studies have described the association of living alone with adverse events in patients with CVD. The Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction (CREDO-KYOTO) registry included patients with acute coronary syndrome (ACS) who underwent PCI; at 5-year follow-up patients living alone did not have an increased risk of death or CV

events, however an increased risk of HF admission. Their study did not show heterogeneity in patients ≥ 75 years.(6) In patients post-ACS from Japan, The Osaka Acute Coronary Insufficiency Study (OACIS) registry showed patients living alone had overall increased MACE, with female patients living alone showing a trend towards increased risk.(13) The Reduction of Atherothrombosis for Continued Health (REACH) Registry was a large, prospective, observational registry with >40,000 patients with high vascular risk and established CVD. Their results showed that living alone was associated with an increased risk of 4-year mortality and CV death in patients with established CVD;(5) there was heterogeneity in risk of events according to age with lower risk in elderly patients >80 years old. In contrast to REACH, our analysis did not show a difference in all-cause and CV death according to living situation, potentially due to several reasons. Compared to REACH, patients included in the CLARIFY registry were younger, had less conventional risk factors and prior history of vascular disease, and represented a lower-risk population evident by the lower event rates for death and CV outcomes. Patients in the CLARIFY registry also were on more guideline-recommended secondary preventative therapy.

The potential sex-specific differences in CV outcomes according to living situation supports previous literature exploring this association (**Table 5**).(5, 7, 14-18)

Table 5. Studies with Sex-specific Differences in Cardiovascular Outcomes According to Living Arrangement in patients with Cardiovascular Disease

Study (Year)	Study Period/Location	Patients included	Outcomes
Case (1992) (17)	1983 – 1986, United States and Canada Randomized control trial (The Multicenter Diltiazem Postinfarction Trial)	Age 25 – 75 years, admitted to hospital with acute myocardial infarction	Women living alone had risk for recurrent cardiac events (HR 2.34, 95% CI 1.17 – 4.66) as compared to men living alone (HR 1.24, 95% CI 0.75.- 2.03)
Kilpi (2015) (14)	1987 – 2007, Finland Population-based study	Men and women living in a private household, previous coronary heart disease	Men living alone had increased risk of long-term mortality compared to married men (OR 1.50, 95% CI 1.29 – 1.75, $p < 0.001$)
Kitamura (2013) (13)	2002 – 2010, Japan Prospective, multicenter observational study	Post-myocardial infarction	Men living alone were associated with a higher risk of recurrent myocardial infarction (HR 1.71, 95% CI 1.11 – 2.64) Women living alone had higher risk of stroke (HR 4.21, 95% CI 1.65 – 10.79)
Lammintausta (2013) (16)	1993 – 2002, Finland Population based registry	Previous myocardial infarction	Men and women living alone had higher case fatality rate. Men living alone received thrombolysis less often than men living with one or more people.
O'Shea (2002) (18)	1995 – 1997, Germany, United States Global Use of Strategies to Open occluded coronary arteries (GUSTO)-III trial.	Patients with acute myocardial infarction	After adjustment, living alone was not an independent risk factor for cardiovascular outcomes with no heterogeneity identified according to gender.

Schmaltz (2007) (7)	1998 – 1999, Canada Retrospective study	Primary discharge diagnosis of acute myocardial infarction	Men living alone had increased risk of death (HR 2.0, 95% CI 1.1-3.7), but not in women (HR 1.2, 95% CI 0.7-2.2).
Udell (2012) (5)	2003 – 2004, 44 countries Prospective study	Prior coronary, cerebrovascular, or peripheral artery disease, and participants without established atherothrombosis but at least 3 CV risk factors (diabetes mellitus, microalbuminuria, ankle-brachial index < 0.9, asymptomatic carotid stenosis of at least 70%, carotid intima media thickness, hypertension, dyslipidemia, current smoking, or age 65 years or older for men or 70 years or older for women).	Living alone was associated with higher all-cause mortality (HR 1.24, p=0.04) and CV death (HR 1.29, p=0.04), however no heterogeneity identified according to sex.

There are several mechanisms that may account for the discrepancy in CV events seen between men and women living alone. Historically, women manage the household and assume a nurturing role, and may develop superior self-care skills than their male counterparts. Women socialize differently than men and may form stronger social networks outside of their cohabitation, relying

less on spousal support compared to men.(19) Men living alone who were previously cohabitating with women may not have developed adequate independent coping mechanisms and social supports. This may lead to poor outreach with less attendance to physician appointments or cardiac rehabilitation, and seeking out medical attention when necessary.(20) Previous studies have shown heterogeneity between men and women in regards to stressful life events and social support and its impact on both health related quality of life, as well as psychological and physical function.(21) The difference in CV risk factors between women living alone and women living with others has not been clearly defined; women living alone may have an increased risk of developing diabetes, are more likely to smoke, and less likely to have hypertension.(20, 22) In the current era, women are more financially and socially independent than previous generations, with technology enhancing accessibility and communication. It may be that living status in women may not be as strong a reflection of social isolation compared to males. These suggestions are speculative as previous studies have failed to show this sex-based interaction identified in the CLARIFY registry.(5, 13, 17, 18, 23) Further studies are warranted to assess factors that may attribute to the difference in CV risk in men and women living alone such as location of residence (urban or rural), social supports, social networks, local health care resources, as well as institutionalization, marital status, and progression of CV risk factors which may guide novel interventions to reduce recurrent CV events in men living alone.

Similar to findings from the REACH registry, we observed trends toward a lower risk of recurrent MI and stroke among elderly patients (≥ 75 years) living alone, while younger patients (< 65 years) living alone had increased risk. Patients < 65 years may have relatively complex social interactions with increased stress, anxiety and depression resulting in poor health behaviour with adverse hemodynamic effects which may lead to the progression of CVD. Elderly patients ≥ 75 years living alone may reflect those who have less comorbid conditions and are able to live independently, and do not require assisted living or nursing home level of care. Discharge planning in elderly patients is multifaceted with a focus on mobility, home safety, and methods to improve medication adherence with early and close outpatient follow-up. Lower CV events in elderly patients living alone may also represent the success of post-discharge initiatives in this patient population. Our analysis suggests that there is not an association between elderly women living alone and increased risk for CV events but there may be in men; this finding is hypothesis generating and further analyses are needed to elucidate the potential mechanisms underlying this difference.

With advancements in the management CAD, patients are living longer with improved health and functional status. For this reason, living situation is an important variable to account for and thus our analysis has several important implications. After adjustment, we did not identify that living alone is associated with an independent risk for MACE in patients with stable CAD. There was similar use of guideline recommended therapy in both living status groups. This

is in contrast to previous studies which suggest that patients living alone may be at increased risk of CV events. This may represent an improvement of care provided by clinicians managing these patients with increased long-term awareness of psychosocial issues, ensuring optimal care is delivered, potentially limiting the care gap in this patient population. Similarly, the suggested lower risk in elderly patients living alone may be a testament to close clinical follow-up and adequacy of social supports provided which allows these individuals to remain living alone in the community without institutionalization. The novel finding of potential lower CV risk in women warrants further assessment. Women living alone may have coping mechanisms that we were not able to identify in our analysis that may have accounted for this difference. As cardiovascular specialists caring for patients with established coronary artery disease, it is important to consider psychosocial factors such as living status which may increase cardiovascular risk. Physicians should counsel patients to report symptoms immediately without delay to medical attention and identify those that may benefit from further psychosocial intervention. Future studies can explore the role of interventional social support, such as cardiac rehabilitation, which may improve outcomes in these subgroups. To date, there is little trial data to show providing multidisciplinary social support improves outcomes following a cardiac event, but several years have passed and new methods of connectivity now exist that may improve effects.

There are several limitations to our analysis. The case report form identified patients living alone at baseline, which we used as a marker of social isolation.

Specific details were not provided about living status including living conditions (type of residence), and proximity of social supports and resources, which may have further differentiated this heterogeneous population. In addition, we were not able to account or adjust for unidentified confounders such as stress, depression, and socioeconomic status. Unfortunately, this information is not available and although we tried to adjust for various patient characteristics, we acknowledge that there remains a potential for residual confounding. Physicians investigators completed the electronic case report form at baseline and yearly entering the patient information. It is unclear if the physician investigator contacted the patient directly or via relatives. Furthermore, study end points were determined by the site investigators without central adjudication. A previous study in young patients with MI demonstrated those with lower social support were more likely to live alone but also had poorer mental health status, quality of life scores, and more depression.(24) Further exploration between living status and mental health outcomes may give insight into this complex interaction. Patients excluded from the CLARIFY registry included those with serious non-cardiovascular disease or conditions interfering with life expectancy (i.e. cancer, drug abuse) or severe cardiovascular disease such as advanced heart failure and were less likely to live alone; the impact this may have had on the analysis is speculative. Our case report form did not identify marital status, which may have given further insight into the heterogeneity of the risk of living alone in females and different age groups. For elderly patients, we were not able to use any other markers of functional status, which may have given further insight into CV risk.

Living status was recorded only at baseline and we were not able to describe how long each patient was living alone or account for the need for change in living status throughout the follow-up period. The case report form only identified clinical end points as described; we were not able to account for other markers of healthcare consumption such as hospitalisation or increased utilization of local health services.

CONCLUSION

Living alone in patients with stable CAD was not associated with an independent increase in MACE, although age and sex-based differences were apparent.

Elderly patients and women living alone may have potentially lower CV risk.

Future large studies in patients with established coronary artery disease should further evaluate key components of social isolation using validated in-depth tools/scoring systems. This will better inform us of higher risk components of social deprivation which will help guide potential psychosocial interventions.

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FIGURE LEGENDS

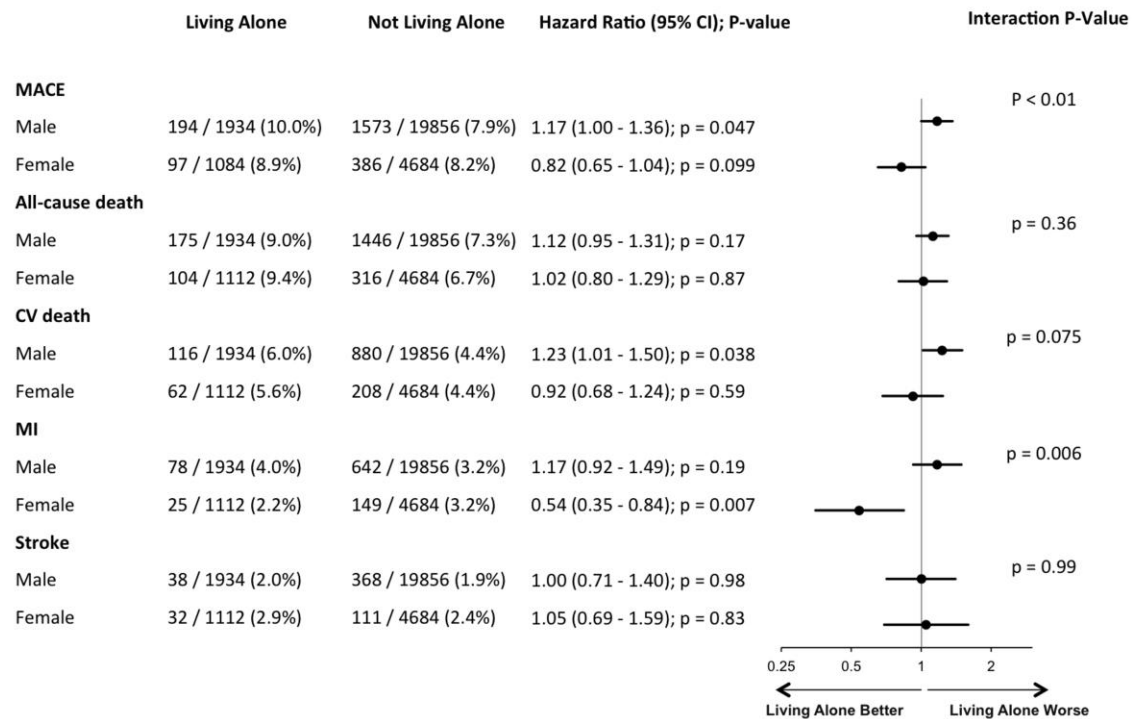


Figure 1: Forest plot: Event Rates, Adjusted Hazard Ratios, and Multivariate interaction by Sex according to Living Arrangement Status

5-year event rate and hazard ratios (HRs) for the primary endpoint of MACE and secondary endpoints (all-cause death, CV death, MI and stroke) stratified by sex according to living arrangement status. Adjusted HRs associated with living alone compared with living with others (reference). The multivariate analysis was adjusted for age, sex, geographical region, smoking status, diabetes, peripheral arterial disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, asthma/chronic obstructive pulmonary disease, congestive heart failure, systolic blood pressure, diastolic blood

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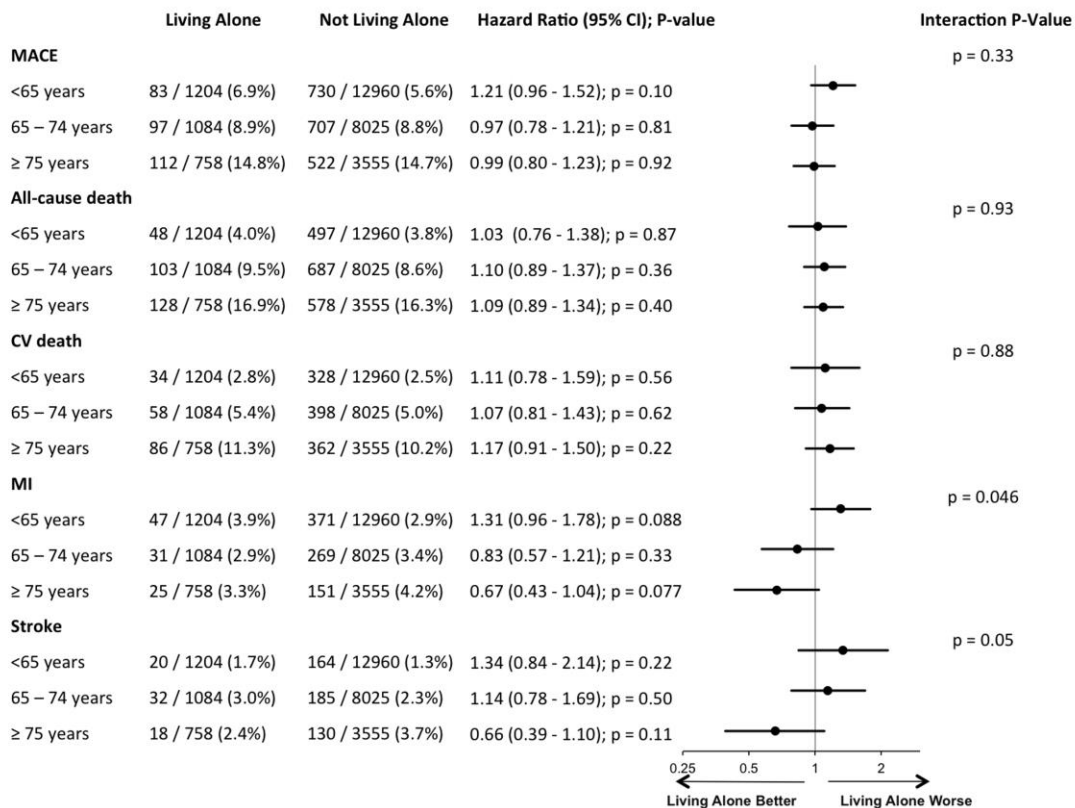


Figure 2: Forest Plot: Event Rates, Adjusted Hazard Ratios, and Multivariate interaction by Age Group according to Living Arrangement Status

5-year event rate and hazard ratios (HRs) for the primary endpoint of MACE and secondary endpoints (all-cause death, CV death, MI and stroke) stratified by age group according to living arrangement status. Adjusted HRs associated with living alone compared with living with others (reference). The multivariate

analysis was adjusted for age, sex, geographical region, smoking status, diabetes, peripheral arterial disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, asthma/chronic obstructive pulmonary disease, congestive heart failure, systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction, number of vessels with coronary artery stenosis.